

University of Dundee

## Higher doses of loop diuretics limit uptitration of angiotensin converting enzyme inhibitors in patients with heart failure and reduced ejection fraction

ter Maaten, Jozine M.; Martens, Pieter ; Damman, Kevin; Dickstein, Kenneth; Ponikowski, Piotr; Lang, Chim

*Published in:*  
Clinical Research in Cardiology

*DOI:*  
[10.1007/s00392-020-01598-w](https://doi.org/10.1007/s00392-020-01598-w)

*Publication date:*  
2020

*Document Version*  
Publisher's PDF, also known as Version of record

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

ter Maaten, J. M., Martens, P., Damman, K., Dickstein, K., Ponikowski, P., Lang, C., Ng, L. L., Anker, S. D., Samani, N. J., Filippatos, G. S., Cleland, J. G. F., Zannad, F., Hillege, H. L., van Veldhuisen, D. J., Metra, M., Voors, A. A., & Mullens, W. (2020). Higher doses of loop diuretics limit uptitration of angiotensin converting enzyme inhibitors in patients with heart failure and reduced ejection fraction. *Clinical Research in Cardiology*, 109(8), 1048-1059. <https://doi.org/10.1007/s00392-020-01598-w>

### **General rights**

Copyright and moral rights for the publications made accessible in Discovery Research Portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from Discovery Research Portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain.
- You may freely distribute the URL identifying the publication in the public portal.

### **Take down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

## **Supplementary material**

### **Higher doses of loop diuretics limit uptitration of angiotensin converting enzyme inhibitors in patients with heart failure and reduced ejection fraction**

Jozine M. ter Maaten, Pieter Martens, Kevin Damman, Kenneth Dickstein, Piotr Ponikowski, Chim C. Lang, Leong L. Ng, Stefan D. Anker, Nilesh J. Samani, Gerasimos Filippatos, John G. Cleland, Faiez Zannad, Hans L. Hillege, Dirk J. van Veldhuisen, Marco Metra, Adriaan A. Voors, Wilfried Mullens

**Supplementary table 1 Multivariable regression log loop diuretic dose at baseline**

	<b>Beta coeff</b>	<b>95% CI</b>	<b>T-value</b>	<b>P-value</b>
<b>eGFR per SD</b>	-0.147	-0.20--0.10	-5.855	<0.001
<b>Renin per SD</b>	0.096	0.06-0.14	4.794	<0.001
<b>Potassium per SD</b>	-0.081	-0.12--0.04	-4.247	<0.001
<b>NT-proBNP per SD</b>	0.082	0.04-0.12	4.154	<0.001
<b>Previous heart failure hospitalization</b>	0.165	0.08-0.25	3.943	<0.001
<b>Hepatomegaly</b>	0.215	0.11-0.35	3.883	<0.001
<b>Diastolic blood pressure per SD</b>	-0.060	-0.10--0.02	-3.054	0.002
<b>Age per SD</b>	-0.066	-0.11--0.02	-2.938	0.003
<b>COPD</b>	0.139	0.04-0.24	2.726	0.006
<b>Urea per SD</b>	0.050	0.01-0.09	2.324	0.020
<b>Atrial fibrillation</b>	0.076	0.00-0.15	1.906	0.057

$R^2=0.144$

**Abbreviations:** COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, NT-proBNP: n terminal pro blood natriuretic peptide, SD: standard deviation

**Supplementary table 2. Clinical characteristics at 9 months over quartiles of loop diuretics at baseline**

	Q1	Q2	Q3	Q4	P-trend
<b>Loop diuretic dose</b>	40 [40-40]	60 [50-60]	80 [80-120]	250 [160-300]	
<b>Clinical profile at 9 months</b>					
<b>Oedema above the knee (%(n))</b>	6.4 (56)	4.5 (4)	10.1 (32)	18.1 (40)	<0.001
<b>Rales &gt; 1/3 up lung fields (%(n))</b>	5.6 (4)	0 (0)	9.8 (4)	7.1 (3)	0.541
<b>Jugular venous pressure (%(n))</b>	5.1 (36)	11.8 (8)	12.1 (32)	12.3 (23)	<0.001
<b>Hepatomegaly (%(n))</b>	4.1 (42)	6.4 (6)	5.1 (19)	10.8 (28)	<0.001
<b>Third heart tone (%(n))</b>	4 (41)	3.2 (3)	2.7 (10)	3.4 (9)	0.386
<b>Orthopnoea (%(n))</b>	8.6 (93)	5.2 (5)	12.5 (48)	12.2 (33)	0.016
<b>NYHA class (%(n))</b>					<0.001
<b>I</b>	14.4 (190)	15 (18)	11.5 (58)	8.6 (34)	
<b>II</b>	49.8 (657)	54.2 (65)	37.1 (187)	31.9 (126)	
<b>III</b>	16.1 (212)	10 (12)	24.2 (122)	24.1 (95)	
<b>IV</b>	0.3 (4)	0.8 (1)	1.2 (6)	2 (8)	
<b>Systolic blood pressure (mmHg)</b>	124.5±19.3	125.3±20.8	125.4±22.4	121.0±21.4	0.031
<b>Diastolic blood pressure (mmHg)</b>	75.0±11.8	75.9±12.0	74.1±13.2	72.0±11.9	<0.001
<b>Heart rate (beats/min)</b>	71.9±15.3	74.4±16.9	72.7±15.7	72.9±15.2	0.713

**Abbreviations:** NYHA: New York Heart Association

**Supplementary table 3. Baseline characteristic decrease/no change/increase of loop diuretics from baseline to 9 months**

	Decrease in dose of loop diuretic	No change in dose of loop diuretic	Increase in dose of loop diuretic	<i>P-trend</i>
<b>N =</b>	745	885	373	
<b>Loop diuretic dose change</b>	-40 [-100--40]	0 [0-0]	40 [30-125]	
<b>Loop diuretic dose at baseline</b>	80 [40-150]	40 [40-40]	40 [40-80]	<0.001
<b>Loop diuretic dose at 9 months</b>	25 [0-40]	40 [40-40]	120 [75-240]	<0.001
<b>Demographics</b>				
<b>Sex (% Male(n))</b>	73.2 (545)	75.8 (671)	75.3 (281)	0.319
<b>Age (years)</b>	67.2±12.7	67.9±11.9	68.9±10.7	0.024
<b>BMI (kg/m2)</b>	28.1±6	27.9±5	28.6±5.6	0.110
<b>Weight (kg)</b>	82.5±20.3	82.5±17.4	83.9±18.3	0.221
<b>NYHA class %(n))</b>				0.829
<b>I</b>	2.4 (18)	3.3 (29)	1.3 (5)	
<b>II</b>	32.9 (245)	45.1 (399)	27.1 (101)	
<b>III</b>	48.6 (362)	41.6 (368)	56.6 (211)	
<b>IV</b>	13.2 (98)	8.1 (72)	12.6 (47)	
<b>LVEF (%)</b>	29.3±7.8	29.4±7.5	28.4±8	0.091
<b>Clinical Profile</b>				
<b>Oedema %(n))</b>	30 (187)	18.5 (132)	35.5 (111)	0.703
<b>Orthopnoea %(n))</b>	37.9 (281)	25.6 (227)	38.4 (143)	0.248
<b>Rales &gt; 1/3 up lung fields %(n))</b>	21.4 (84)	15.7 (58)	18 (37)	0.178
<b>Jugular venous pressure %(n))</b>	33.7 (174)	22.7 (132)	40.3 (94)	0.671
<b>Hepatomegaly %(n))</b>	13.1 (97)	9.8 (87)	18.9 (70)	0.061
<b>Third heart tone %(n))</b>	9.9 (73)	8.2 (72)	12.6 (47)	0.319
<b>Systolic Blood Pressure (mmHg)</b>	124.4±22.2	127.5±20.6	122±21.4	0.080
<b>Diastolic Blood Pressure (mmHg)</b>	75.6±14.5	76.8±12.9	74.3±11.8	0.126
<b>Heart Rate (beats/min)</b>	81.8±20.4	78.2±19.1	79.7±17.9	0.090
<b>Hospitalization</b>				

Type of visit (%(n))				0.009
Scheduled outpatient	22.6 (168)	39.1 (346)	25.7 (96)	
Unscheduled outpatient	4.7 (35)	7.6 (67)	5.4 (20)	
Inpatients hospitalization	72.8 (542)	53.3 (472)	68.9 (257)	
Reason for visit (%(n))				0.154
Worsening heart failure	51.1 (381)	50.1 (443)	60.9 (227)	
New-onset heart failure	32.8 (244)	26.2 (232)	22.8 (85)	
Other reason	16.1 (120)	23.7 (210)	16.4 (61)	
Heart Failure History				
Years since first diagnosis	3 [0.5-6.4]	1.1 [0.3-6.7]	2 [0.3-6.5]	0.920
Ischemic heart disease (%(n))	56.7 (368)	62.3 (497)	62.3 (210)	0.045
Previous HF hospitalization (%(n))	30.6 (228)	27.9 (247)	37.8 (141)	0.067
Medical History				
Hypertension (%(n))	58.9 (439)	62.8 (556)	66 (246)	0.017
Atrial fibrillation (%(n))	44.2 (329)	38.5 (341)	50.4 (188)	0.252
Diabetes mellitus (%(n))	29.1 (217)	30.1 (266)	39.9 (149)	0.001
Laboratory				
Creatinine (umol/L)	100 [84.5-126]	97 [79.6-119]	105 [84.5-133.5]	0.060
Urea (mmol/L)	11.2 [7.5-18.6]	9.3 [6.7-14.8]	12.1 [8-18.6]	0.875
eGFR (ml/min/1.73m2)	61.8 [45.8-78.7]	64.1 [48.6-83.5]	58.6 [44.2-76.1]	0.108
Sodium (mmol/L)	140 [137-142]	140 [138-142]	140 [137-142]	0.854
Potassium (mmol/L)	4.2 [3.9-4.5]	4.3 [4-4.7]	4.2 [3.9-4.6]	0.566
Albumin (g/L)	33 [28-38]	34 [29-39]	32 [27-38]	0.842
Aldosterone (pg/mL)	92.9 [41-187]	96 [48-200.2]	102.7 [48.8-217.8]	0.059
Renin (UI/mL)	88.7 [30.2-249.8]	72.8 [25.2-204.9]	118.8 [33.1-303.3]	0.934
NT-proBNP (pg/mL)	2731 [1200-5923]	1942 [789.3-4143]	2918 [1442.5-6313.5]	0.853
Clinical characteristics at 9 months				
Oedema above the knee (%(n))	8 (40)	6.7 (47)	15 (45)	0.005

<b>Rales &gt; 1/3 up lung fields (%(n))</b>	11.3 (6)	4.3 (3)	4.7 (2)	0.170
<b>Jugular venous pressure (%(n))</b>	7.1 (30)	4.8 (27)	17.1 (42)	<0.001
<b>Hepatomegaly (%(n))</b>	3.6 (21)	4.7 (39)	10.1 (35)	<0.001
<b>Third heart tone (%(n))</b>	2.2 (13)	3.3 (27)	6.6 (23)	0.001
<b>Orthopnoea (%(n))</b>	8.3 (51)	8.6 (73)	15.2 (55)	0.002
<b>NYHA class (%(n))</b>				<0.001
<b>I</b>	19.5 (145)	14.5 (128)	7.2 (27)	
<b>II</b>	42.3 (315)	60.5 (535)	49.3 (184)	
<b>III</b>	17.3 (129)	19.2 (170)	38.1 (142)	
<b>IV</b>	1.3 (10)	0.9 (8)	0.3 (1)	
<b>Systolic blood pressure (mmHg)</b>	125.7±21.5	124.8±19.5	120.4±20.1	<0.001
<b>Diastolic blood pressure (mmHg)</b>	75.0±12.8	74.7±11.9	72.8±11.6	0.008
<b>Heart rate (beats/min)</b>	72.2±15.6	711.6±14.8	74.6±16.5	0.018

**Abbreviations:** BMI: body mass index, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, NT-proBNP: n terminal pro blood natriuretic peptide, NYHA: New York Heart Association

**Supplementary table 4: Doses of beta-blockers at baseline, 3 months and 9 months over quartiles of loop diuretic doses at baseline**

	Q1	Q2	Q3	Q4	P-trend
<b>N =</b>	1319	120	504	395	
<b>Loop diuretic dose</b>	40 [40-40]	60 [50-60]	80 [80-120]	250 [160-300]	
<b>Beta-blockers</b>					
<b>Beta-blockers at baseline %(n)</b>	84.5 (1115)	84.2(101)	81.3 (410)	85.3(337)	0.640
Target dose at baseline %(n)	5.8 (77)	3.3 (4)	5.4 (27)	4.8 (19)	0.421
Percentage of target dose at baseline (%)	20 [10-50]	10 [10-20]	10 [0-30]	20 [10-50]	0.560
<b>Beta-blockers at 3 months %(n)</b>	93.2 (1229)	94.2 (113)	90.9 (458)	88.9 (351)	0.004
Target dose at 3 months %(n)	14.0 (185)	16.7 (20)	10.3 (52)	9.9 (39)	0.008
Percentage of target dose at 3 months (%)	20 [10-50]	20 [10-50]	20 [10-50]	20 [10-50]	0.063
Change in percentage of target dose from baseline to 3 months (%) <sup>#</sup>	0 [0-16.7]	4.2 [0-25]	0 [0-16.7]	0 [0-12.5]	0.056
<b>Beta-blockers at 9 months %(n)</b>	93.5 (1233)	92.5 (111)	90.1 (454)	87.6 (346)	<0.001
Target dose at 9 months %(n)	16.5 (217)	20.8 (25)	11.1 (56)	11.9 (47)	0.002
Percentage of target dose at 9 months (%)	20 [10-50]	20 [10-50]	20 [10-50]	20 [10-50]	0.001
Change in percentage of target dose from baseline to 9 months (%) <sup>#</sup>	0 [0-25]	8.3 [0-25]	0 [0-21]	0 [0-12.5]	0.001

<sup>#</sup>Defined as: percentage of target dose at 3 months minus percentages of target dose at baseline divided by percentage of target dose at baseline times 100



**Supplementary table 5: Loop diuretic dose and beta-blockers over time**

Log loop diuretic dose (per doubling)	Beta-blocker use at 3 months		Target dose at 3 months		Change in percentage of target dose from baseline to 3 months		Change in percentage of target dose from baseline to 9 months	
	OR (CI)	P-value	OR (CI)	P-value	Beta (CI)	P-value	Beta (CI)	P-value
<b>Univariable</b>	0.86 (0.77-0.98)	0.020	0.87 (0.78-0.97)	0.015	-0.77 (-1.54 - -0.02)	0.044	-1.86 (-2.79 - -0.92)	<0.001
<b>Multivariable<sup>^</sup></b>	0.87 (0.77-0.99)	0.027	0.88 (0.79-0.98)	0.019	-0.70 (-1.46 - 0.05)	0.068	-1.77 (-2.70 - -0.84)	<0.001
<b>Multivariable<sup>#</sup></b>	0.88 (0.78-1.00)	0.059	0.84 (0.73-0.97)	0.017	-0.83 (-1.62 - -0.04)	0.041	-1.97 (-2.95 - -0.99)	<0.001
<b>Multivariable<sup>*</sup></b>	0.80 (0.68-0.93)	0.003	0.88 (0.76-1.01)	0.069	-0.70 (-1.51 - 0.11)	0.089	-1.60 (-2.59 - -0.60)	0.002
<b>Propensity score adjusted</b>	0.89 (0.77-1.03)	0.111	0.88 (0.76-1.01)	0.069	-0.15 (-1.13 - 0.82)	0.755	-0.59 (-1.76 - 0.57)	0.318

<sup>#</sup> adjusted for sex, country, BMI, AF, and eGFR

<sup>\*</sup> adjusted for log NTproBNP, eGFR, age, sex, and beta-blocker use at baseline

**Abbreviations:** AF: alkaline phosphatase, BMI: body mass index, CI: confidence interval, DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate, HR: heart rate, NT-proBNP: n terminal pro blood natriuretic peptide

**Supplementary table 6: Baseline characteristics over tertiles of congestion score at baseline**

	<b>T1</b>	<b>T2</b>	<b>T3</b>	<b>P-trend</b>
<b>N =</b>	468	542	409	
<b>Congestion score</b>	0 [0-0]	1 [0.3-1.3]	2.3 [1.67-2.67]	
<b>Demographics</b>				
<b>Sex (% Male(n))</b>	78 (365)	76.8 (416)	73.8 (302)	0.153
<b>Age (years)</b>	66.6±11.8	68.1±11.2	69.9±11.7	<0.001
<b>NYHA class %(n))</b>				<0.001
<b>I</b>	3 (14)	0.9 (5)	0.5 (2)	
<b>II</b>	61.5 (288)	32.1 (174)	7.8 (32)	
<b>III</b>	33.1 (155)	57.2 (310)	62.8 (257)	
<b>IV</b>	1.3 (6)	9 (49)	26.2 (107)	
<b>LVEF (%)</b>	29.7±7.2	28.2±8.2	28.3±8.3	0.014
<b>Clinical Profile</b>				
<b>Oedema %(n))</b>	0 (0)	14.4 (78)	68.5 (280)	<0.001
<b>Orthopnoea %(n))</b>	0 (0)	32.5 (176)	77.5 (317)	<0.001
<b>Rales &gt; 1/3 up lung fields %(n))</b>	12.1 (15)	15.7 (44)	27.4 (83)	<0.001
<b>Jugular venous pressure %(n))</b>	0 (0)	22.1 (120)	85.1 (348)	<0.001
<b>Hepatomegaly %(n))</b>	5.8 (27)	13.7 (74)	33.7 (138)	<0.001
<b>Third heart tone %(n))</b>	6.8 (32)	11.8 (64)	15.9 (65)	<0.001
<b>Systolic Blood Pressure (mmHg)</b>	125.2±18.8	123.5±22.4	122.2±22.2	0.040
<b>Diastolic Blood Pressure (mmHg)</b>	76.3±11.5	75.2±13.8	73.4±14.3	0.001
<b>Heart Rate (beats/min)</b>	74.6±16.6	81.9±19.9	84.3±20.5	<0.001
<b>ACE-inhibitors or Angiotensin receptor blockers</b>				
<b>ACE-inhibitors or Angiotensin receptor blockers at baseline %(n))</b>	75.4 (353)	77.5 (420)	70.2 (287)	0.088
<b>Target dose at baseline%(n))</b>	20.7 (73)	18.6 (78)	17.1 (49)	0.242
<b>Percentage of target dose at baseline (%)</b>	20 [10-50]	20 [10-50]	20 [0-50]	<0.001

<b>ACE-inhibitors or Angiotensin receptor blockers at 3 months (%(n))</b>	92.7 (434)	91.1 (494)	82.2 (336)	<0.001
Target dose at 3 months (%(n))	28.3 (123)	24.3 (120)	22.9 (77)	0.078
Percentage of target dose at 3 months (%)	50 [20-100]	50 [20-70]	20 [10-50]	<0.001
<b>ACE-inhibitors or Angiotensin receptor blockers at 9 months (%(n))</b>	92.1 (431)	89.7 (486)	79 (323)	<0.001
Target dose at 9 months (%(n))	30.2 (130)	27.8 (135)	22.3 (72)	0.018
Percentage of target dose at 9 months (%)	50 [20-100]	50 [20-80]	20 [10-50]	<0.001
<b>Mineralocorticoid antagonists</b>				
<b>MRA at baseline (%(n))</b>	59.8 (280)	56.5 (306)	58.7 (240)	0.698
Target dose at baseline (%(n))	16.0 (40)	19.3 (55)	24.8 (56)	0.017
Percentage of target dose at baseline (%)	50 [50-50]	50 [50-50]	50 [50-68.8]	0.285
<b>MRA at 9 months (%(n))</b>	61.9 (255)	61.2 (274)	63.4 (189)	0.715
Target dose at 9 months (%(n))	16.0 (42)	16.1 (49)	20.4 (45)	0.224
Percentage of target dose at 9 months (%)	50 [25-50]	50 [25-50]	50 [25-50]	0.977
<b>Loop diuretics</b>				
<b>Loop diuretic dose at baseline</b>	40 [40-75]	40 [40-115]	80 [40-150]	<0.001
<b>Loop diuretic dose at 9 months</b>	40 [40-60.6]	40 [40-80]	75 [40-120]	<0.001
<b>Percentage loop diuretic dose change</b>	0 [-50-0]	0 [-50-0]	0 [-60-20]	0.011
<b>Loop diuretic use 9 months (%)</b>	88.3 (364)	90.4 (405)	93.3 (278)	0.028
<b>Laboratory</b>				
<b>eGFR (ml/min/1.73m2)</b>	64.7 [48.8-82.7]	60.5 [47.2-77.8]	52 [37.2-70.1]	<0.001
<b>NT-proBNP</b>	1588 [615.6-3375]	2696 [1205-5741]	4602 [2510.5-9321]	<0.001
<b>Clinical Profile at 9 months</b>				
<b>Oedema (%(n))</b>	2.7 (10)	8.8 (34)	12.6 (31)	<0.001
<b>Rales &gt; 1/3 up lung fields (%(n))</b>	6.9 (2)	6.7 (3)	3.6 (1)	0.596
<b>Jugular venous pressure (%(n))</b>	4.9 (16)	7.3 (25)	15.5 (34)	<0.001
<b>Hepatomegaly (%(n))</b>	3.1 (12)	5.4 (23)	10.3 (28)	<0.001
<b>Orthopnoea (%(n))</b>	4 (16)	8.8 (39)	13.6 (39)	<0.001

Third heart tone (%(n))	2.3 (9)	4.4 (19)	4 (11)	0.204
Systolic Blood Pressure (mmHg)	125.6±20.1	123±20.5	123.2±19.7	0.136
Diastolic Blood Pressure (mmHg)	75.3±11.5	73.9±12	73.7±12.9	0.088
Heart Rate (beats/min)	70.8±14.8	71.7±13.9	74.8±14.9	0.001
NYHA class (%(n))				<0.001
I	16 (75)	11.1 (60)	8.3 (34)	
II	54.1 (253)	47 (255)	35.7 (146)	
III	14.5 (68)	20.8 (113)	22.5 (92)	
IV	0 (0)	1.7 (9)	0.7 (3)	
Clinical congestion score	1 [1-1]	1 [1-2]	1 [1-3]	<0.001

**Abbreviations:** BMI: body mass index, eGFR: estimated glomerular filtration rate, LVEF: left ventricular ejection fraction, MRA: mineralocorticoid antagonists, NT-proBNP: n terminal pro blood natriuretic peptide, NYHA: New York Heart Association

**Supplementary table 7: Groups based on change in congestion score and loop diuretic dose at 9 months**

	Decrease in clinical congestion score from baseline to 9 months				No change/increase in clinical congestion score from baseline to 9 months			
	Low dose LD	Medium dose LD	High dose LD	<i>P-trend</i>	Low dose LD	Medium dose LD	High dose LD	<i>P-trend</i>
<b>N =</b>	87	200	161		101	162	141	
<b>Change in congestion score</b>	-1 [-1.3--0.67]	-1.3 [-1.67--1.0]	-1.3 [-2.0--1.0]		0 [0-0]	0 [0-0]	0 [0-0.3]	
<b>Loop diuretic dose at 9 months</b>	20 [0-20]	40 [40-40]	120 [80-200]		20 [0-25]	40 [40-40]	125 [80-175]	
<b>ACE-inhibitors or Angiotensin receptor blockers</b>								
<b>ACE-inhibitors or Angiotensin receptor blockers at baseline (%(n))</b>	80.5 (70)	75 (150)	70.8 (114)	0.095	77.2 (78)	87 (141)	80.9 (114)	0.607
Target dose at baseline (%(n))	12.9 (9)	21.3 (32)	20.2 (23)	0.291	10.3 (8)	28.4 (40)	10.5 (12)	0.638
Percentage of target dose at baseline (%)	20 [10-50]	20 [10-50]	20 [0-50]	0.911	20 [10-50]	50 [20-70]	20 [10-50]	0.352
<b>ACE-inhibitors or Angiotensin receptor blockers at 3 months (%(n))</b>	92 (80)	94 (188)	85.1 (137)	0.029	91.1 (92)	97.5 (158)	92.9 (131)	0.722
Target dose at 3 months (%(n))	23.8 (19)	26.1 (49)	21.9 (30)	0.653	31.5 (29)	34.2 (54)	22.1 (29)	0.089
Percentage of target dose at 3 months (%)	50 [20-80]	50 [20-80]	40 [10-50]	0.085	50 [20-100]	50 [20-100]	40 [20-60]	0.068
<b>ACE-inhibitors or Angiotensin receptor blockers at 9 months (%(n))</b>	90.8 (79)	93.5 (187)	84.5 (136)	0.044	93.1 (94)	97.5 (158)	87.2 (123)	0.041
Target dose at 9 months (%(n))	27.8 (22)	31 (58)	25 (34)	0.522	35.1 (33)	32.9 (52)	25.2 (31)	0.106
Percentage of target dose at 9 months (%)	50 [20-100]	50 [20-100]	30 [10-60]	0.034	50 [20-100]	50 [20-100]	20 [10-60]	0.001
<b>Mineralocorticoid antagonists</b>								
<b>MRA at baseline (%(n))</b>	54.0 (47)	54.0 (108)	67.1 (108)	0.020	43.6 (44)	65.4 (106)	66 (93)	0.001
Target dose at baseline (%(n))	7.3 (3)	15 (16)	29.5 (28)	0.001	8.8 (3)	10.4 (11)	21.0 (17)	0.038
Percentage of target dose at baseline (%)	50 [50-50]	50 [50-50]	50 [50-100]	0.003	50 [50-50]	50 [50-50]	50 [50-50]	0.027
<b>MRA at 9 months (%(n))</b>	47.7 (41)	65.0 (130)	77.6 (125)	<0.001	39.6 (40)	72.8 (118)	62.4 (88)	0.002
Target dose at 9 months (%(n))	13.7 (7)	19.1 (27)	21.6 (25)	0.256	9.3 (4)	13.7 (17)	16.5 (15)	0.269
Percentage of target dose at 9 months (%)	50 [0-50]	50 [50-50]	50 [50-50]	0.013	25 [0-50]	50 [50-50]	50 [25-50]	0.129
<b>Loop diuretics</b>								
<b>Loop diuretic dose at baseline</b>	40 [40-60]	40 [40-80]	100 [40-175]	<0.001	40 [25-40]	40 [40-40]	80 [40-150]	<0.001

<b>Percentage loop diuretic dose change</b>	-75 [-100--50]	0 [-50-0]	0 [-16.7-100]	<0.001	-50 [-100-0]	0 [0-0]	0 [0-100]	<0.001
<b>Clinical Profile at 9 months</b>								
<b>Systolic Blood Pressure (mmHg)</b>	129.3±22.7	123.8±19.4	121.5±19	0.005	126.9±20.7	127.1±19.7	120.8±21.2	0.015
<b>Diastolic Blood Pressure (mmHg)</b>	75.4±13.1	75.2±12.6	72.7±11.5	0.064	75.5±11.7	76.7±11.2	72.5±11.4	0.026
<b>Heart Rate (beats/min)</b>	71.7±14.1	73±13.2	73.6±12.9	0.296	71.1±14.8	71.2±13.8	72.4±15.5	0.474
<b>NYHA class (%(n))</b>				<0.001				<0.001
<b>I</b>	27.6 (24)	14 (28)	8.1 (13)		33.7 (34)	9.3 (15)	7.8 (11)	
<b>II</b>	59.8 (52)	64 (128)	54 (87)		51.5 (52)	74.1 (120)	43.3 (61)	
<b>III</b>	11.5 (10)	19.5 (39)	35.4 (57)		13.9 (14)	14.8 (24)	44.7 (63)	
<b>IV</b>	0 (0)	0.5 (1)	0.6 (1)		0 (0)	1.9 (3)	3.5 (5)	
<b>Clinical congestion score</b>	0 [0-0]	0 [0-0]	0 [0-0.3]	<0.001	0 [0-0]	0 [0-0]	0.3 [0-1]	<0.001
<b>Haematocrit (%)</b>	39.2 [36.0-43.2]	40.1 [37.5-43.0]	40.0 [36.0-42.9]	0.786	41.5 [38.5-44.0]	40.5 [38.5-43.6]	38.9 [35.0-42.0]	0.002
<b>BUN/creatinine ratio</b>	12.2 [6.2-16.4]	11.8 -8.3-14.8]	9.6 [5.4-12.5]	0.002	9.8 [5.9-14.0]	12.1 [9.9-15.0]	9.8 [6.2-12.8]	0.450

**Abbreviations:** ACE: angiotensin converting enzyme, BUN: blood urea nitrogen, NYHA: New York Heart Association, LD: loop diuretics

**Supplementary table 8. Cox regression analysis for the combined endpoint of all-cause mortality and heart failure hospitalization**

	Combined endpoint			
	Univariable		Multivariable <sup>#</sup>	
	HR (95% CI)	P-value	HR (95% CI)	P-value
<b>Log loop diuretic dose</b>	1.71 (1.58-1.85)	<0.001	1.16 (1.06-1.27)	0.002
<b>Low dose (&lt;80 mg of furosemide)</b>	Ref	Ref	Ref	Ref
<b>High dose (≥80 mg of furosemide)</b>	1.92 (1.69-2.19)	<0.001	1.25 (1.09-1.42)	<0.001
<b>Low dose &amp; ≥50% of ACEi target dose</b>	Ref	Ref	Ref	Ref
<b>Low dose &amp; &lt;50% of ACEi target dose</b>	1.39 (1.12-1.73)	0.003	1.04 (0.83-1.30)	0.726
<b>High dose &amp; &lt;50% of ACEi target dose</b>	2.82 (2.28-3.48)	<0.001	1.38 (1.09-1.73)	0.006
<b>High dose &amp; ≥50% of ACEi target dose</b>	1.71 (1.36-2.15)	<0.001	1.22 (0.97-1.55)	0.090

<sup>#</sup> adjusted for the BIOSTAT risk model for the combined endpoint (age, HF hospitalization in previous year, systolic blood pressure, log NT-proBNP, hemoglobin, high-density lipoprotein, sodium, and beta-blocker use at baseline)

*Abbreviations:* ACEi: angiotensin converting enzyme inhibitors, CI: confidence interval, HR: hazard ratio.